N-aryl benzisoselenazolones – synthesis, transformations and antioxidant activity

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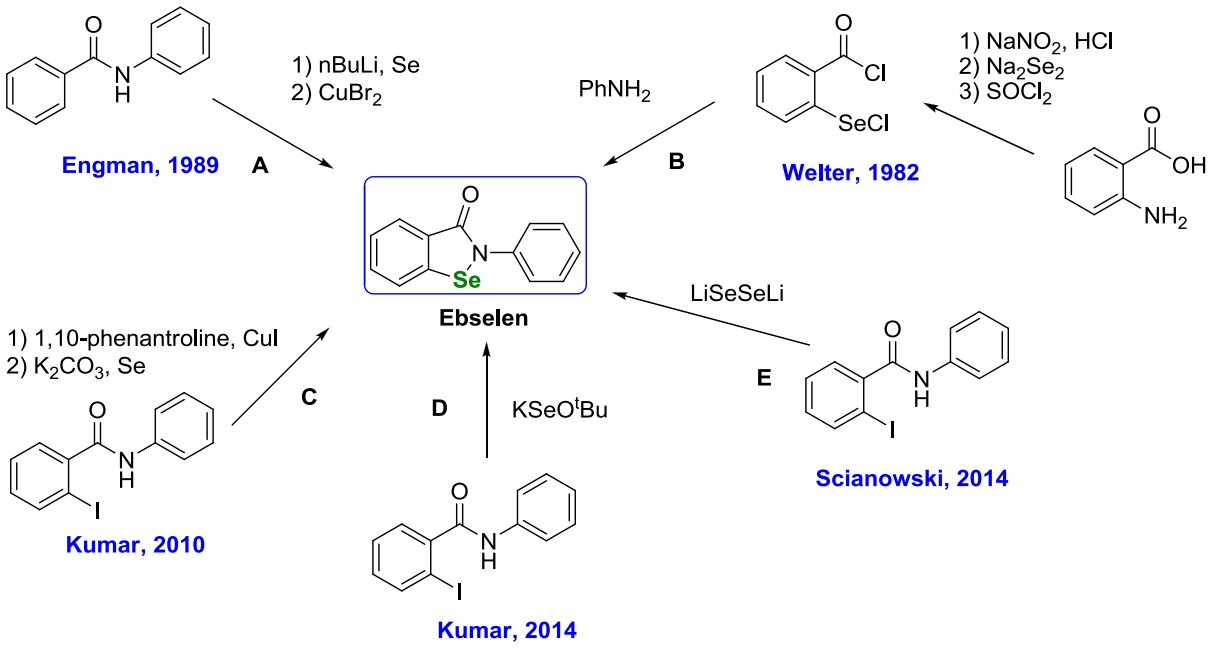
Abstract: The applicability of organoselenium compounds in medicinal chemistry arises from their unique biological properties, among which the antioxidant activity seems to be the leading one. Since ebselen (*N*-phenyl-1,2-benzisoselenazol-3(2*H*)-one) has been proven to mimic the activity of the antioxidant enzyme glutathione peroxidase GPx, the search for more effective peroxide scavengers has become a 'hot topic' in this field of research. Herein, we present the synthesis of *N*-aryl ebselen derivatives, bearing additional electron donating or electron withdrawing groups in the N-phenyl ring, by two methods: (a) reaction of *N*-substituted *o*-iodobenzamides with lithium diselenide, (b) synthesis based on the formation of 2,2-diselenobis(benzoic acid), followed by the conversion to corresponding dichloride and further reaction with amine. Significant improvements in these methodologies are highlighted. All obtained ebselen derivatives were further converted to corresponding diselenides by the treatment with sodium borohydride. The antioxidant potential of the obtained selenium derivatives and conclusions concerning the activity-structure relation are presented.

Keywords: ebselen, benzisoselenazol-3(2*H*)-ones, diselenides, antioxidant activity

Introduction

Through the years, ebselen was thoroughly studied and evaluated as a potent hydroperoxide reducing agent, applicable in diseases caused by oxidative stress. The combination of significant pharmacological potential and low toxicity *in vivo* induced numerous studies on its mechanism of action, biochemical effects and therapeutic application and also several clinical trials. Currently, numerous research articles and reviews indicate that the search for new "ebselen-like" therapeutics has regained much attention [1].

There are several methodologies to synthesize ebselen and its derivatives. *o*-Metalation of *N*-phenylbenzamide, selenium insertion and oxidative cyclization by copper bromide (**A**) [2], a multi-step synthesis based on the formation of 2,2-diselenobis(benzoic acid), followed by the conversion to corresponding dichloride with thionyl chloride and further reaction with aniline (**B**) [3], and treatment of *N*-phenyl *o*-iodobenzamide with different nucleophiles generated in the reaction of a copper catalyst and selenium in the presence of potassium carbonate as base (**C**)[4], from selenium and potassium *tert*-butoxide (**D**) [5] or by the methodology presented in our previous paper in which lithium diselenide, formed in the reaction of lithium hydroxide and elemental selenium in the presence of hydrazine hydrate, is applied (**E**) [6] (Scheme 1).

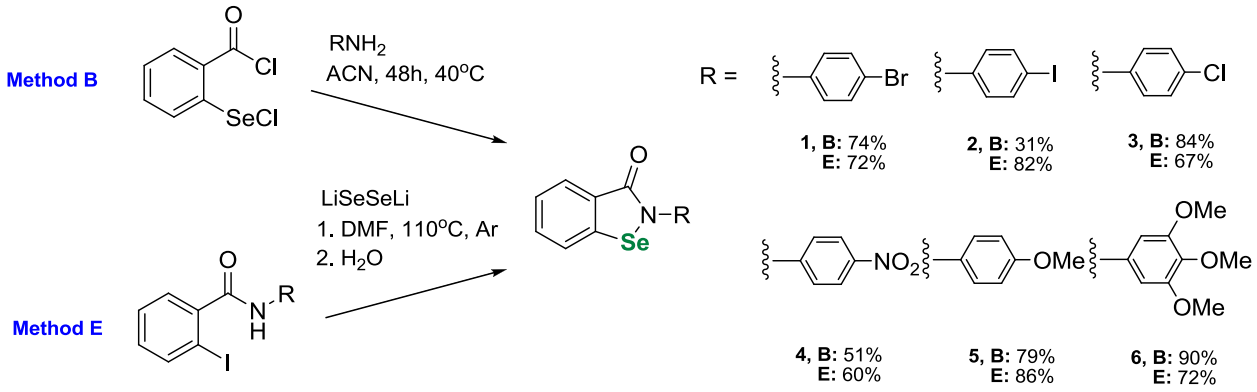


Scheme 1. Methods of ebselen synthesis

In this communication we present new insights to the previously published by our research group method **E**, including the modulation of the final reaction product by the presence of water. Additionally, we will present that specific purification method to improve the overall yield of the reaction **B**. All synthesized *N*-aryl benzisoselenazolones and corresponding diselenides will be also evaluated as antioxidants.

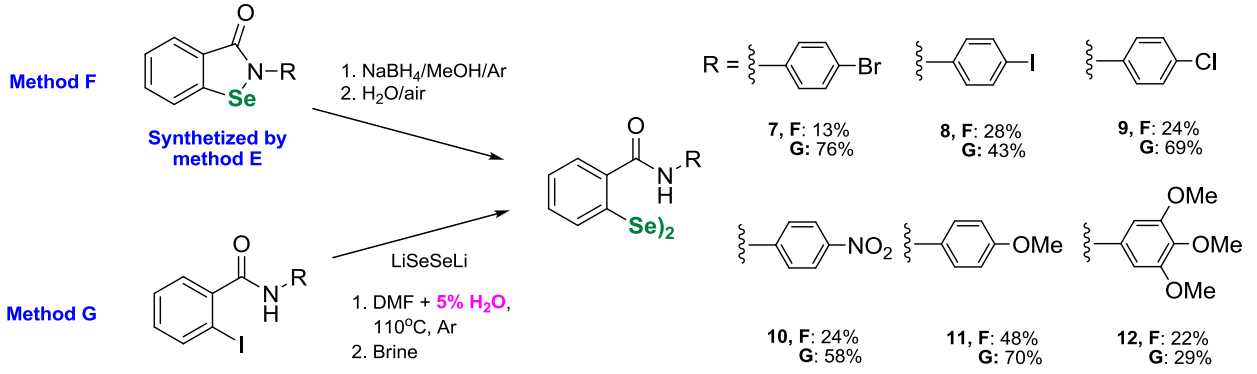
Results and discussion

First, we have synthetized a series of *N*-arylbenzisoselenazolones **1**-**6** by our previously presented methodology (**E**). Second goal was to obtain same derivatives applying the most common in the literature method **B** and compare the efficiency of the reactions. Although the methodology presented by Welter is highly useful for a broad scope of different amines, the overall yield of the reaction is in most cases low. This is caused by the common formation of Na_2Se, beside the desired Na_2Se_2 and additionally the presence of salicylic acid as a by-product in the synthesis of 2,2-diselenobis(benzoic acid). Multiple rinsing of the crude product with boiling water enabled us to eliminate salicylic acid and obtain the final product as pure solid in 90% yield. Results of both methods **B** and **E** are presented in Scheme 2.



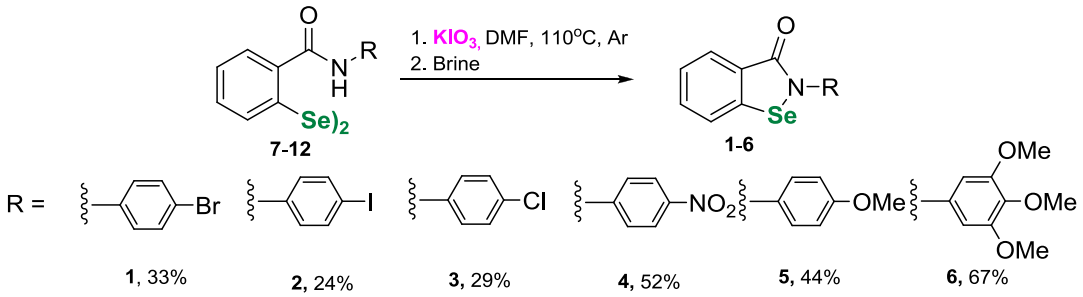
Scheme 2. Synthesis of ebselen derivatives using procedure **B** and **E**

Next, we have transformed benzisoselenazolones **1-6** to corresponding diselenides **7-12**. Reduction with sodium borohydride (procedure **F**) enabled to obtain compounds **7-12** in only low to moderate yields. We have further established that by adding 5% of water to the DMF used in the synthesis of benzisoselenazolones by our previously presented methodology (**E**), we can obtain pure diselenides **7-12** in significantly higher yields (29-70%) (Scheme 3).



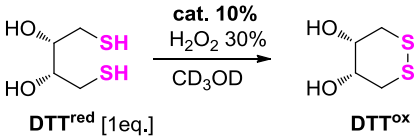
Scheme 3. Synthesis of diselenides **7-12**

In reduced diselenides **7-12** we were also able to regenerate the Se-N bond by oxidative cyclization with potassium iodate (Scheme 4).



Scheme 4. Synthesis of benzisoselenazolones **1-6**

The ability to eliminate peroxides was tested by a NMR assay where dithiol (DTT^{red}) is transformed to a disulphide (DTT^{ox}) by a selenocatalyst in the presence of hydrogen peroxide [7]. The rate of the reaction was measured from the changes in the ^1H NMR spectrum (Table 1).



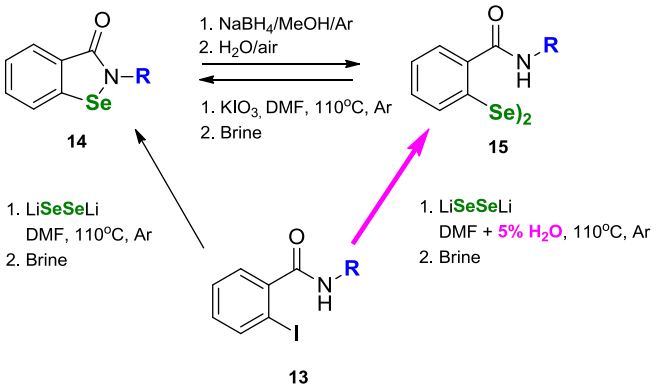
	Remaining Dithiotreitol [%]				
Catalyst [0.1 equiv.]	3 min	5 min	15 min	30 min	60 min
Benzisoselenazolones					
1	86	83	79	75	71
2	**42**	**0**	**0**	**0**	**0**
3	78	68	50	38	36
4	25	7	5	0	0
5	64	41	5	0	0
6	**5**	**0**	**0**	**0**	**0**
Ebselen	84	75	64	58	52
Diselenides					
7	81	72	55	41	23
8	89	83	81	78	74
9	61	53	26	19	21
10	**100**	**0**	**0**	**0**	**0**
11	84	73	63	57	52
12	96	82	41	6	0

Table 1. Activity of the tested catalysts

The highest activity was observed for benzisoselenazolone **2** and **6** bearing an iodine atom in the *para* position of the *N*-phenyl ring and three methoxy groups, respectively and also diselenide **10** with a nitro group. For both derivatives total conversion of the substrate was observed after 5 minutes of the reaction.

Conclusion

All improvements and possible reaction paths of the previously presented method **E** are summarized in Scheme 5. A new highly efficient method to obtained substituted diselenides has been developed. By adding 5% of water we were able to obtain pure diselenides **15** and in the absence of water – benzisoselenazolones **14**.



Scheme 5. Summary of the developed procedures

Developed procedures were applied for the synthesis of a series of *N*-aryl benzisoselenazolones and corresponding diselenides. Ebselen derivatives have been synthetized by two routes: according to our previously presented methodology and by the reaction of an amine with 2-(chloroseleno)benzoyl chloride. Obtained results were comparable. Correspodnig diselenides had been also synthetized by two procedures: reduction of benzisoselenazolones with $NaBH_4$ and the newly presented methodology **F** for which, in all cases, yields were significantly higher. All compounds were evaluated as antioxidants. The best activity was observed for benzisoselenazolone **2** and diselenide **10**.

Acknowledgments

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References

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